

Variant: *NM_004333.6(BRAF):c.1455G>C (p.Leu485Phe)*

Version: 1.5

CA273414 [↗](#)

13975 (ClinVar) [↗](#)

Gene: BRAF ([HGNC:673](#))

Condition: RASopathy ([MONDO:0021060](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: d7b34568-d590-44cf-a60c-e208532866d3

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HGVS expressions

NM_004333.6(BRAF):c.1455G>C (p.Leu485Phe)

NM_004333.6:c.1455G>C

NC_000007.14:g.140778053C>G

CM000669.2:g.140778053C>G

NC_000007.13:g.140477853C>G

CM000669.1:g.140477853C>G

NC_000007.12:g.140124322C>G

NG_007873.3:g.151712G>C

ENST00000646891.2:c.1455G>C

ENST00000288602.11:c.1575G>C

ENST00000479537.6:c.125G>C

ENST00000496384.7:c.1455G>C

ENST00000497784.2:c.*905G>C

ENST00000642228.1:c.*533G>C

ENST00000642875.1:n.1019G>C

ENST00000644120.1:n.1845G>C

ENST00000644650.1:c.551G>C

ENST00000644905.1:n.1544G>C

ENST00000644969.2:c.1575G>C

ENST00000646730.1:c.1455G>C

ENST00000646891.1:c.1455G>C

ENST00000647434.1:c.498G>C

ENST00000288602.10:c.1455G>C

ENST00000496384.6:c.278G>C

ENST00000497784.1:c.1490G>C

NM_004333.4:c.1455G>C

NM_001354609.1:c.1455G>C

NM_004333.5:c.1455G>C

NR_148928.1:n.1760G>C

NM_001354609.2:c.1455G>C

NM_001374244.1:c.1575G>C

NM_001374258.1:c.1575G>C

NM_001378467.1:c.1464G>C

NM_001378468.1:c.1455G>C

NM_001378469.1:c.1389G>C

NM_001378470.1:c.1353G>C

NM_001378471.1:c.1344G>C

NM_001378472.1:c.1299G>C
NM_001378473.1:c.1299G>C
NM_001378474.1:c.1455G>C
NM_001378475.1:c.1191G>C

Pathogenic

Met criteria codes 6

PS2 PS3 PS4_Moderate PP2
PP3 PM2

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1455G>C (p.Leu485Phe) variant in BRAF is absent from gnomAD (PM2). It has been detected in at least 4 patients with clinical features of a RASopathy, 1 of which was reported as a de novo case with parentage confirmation (PS4_Moderate; PS2; 19206169, 16474404, SCV000197149.4). In vitro functional studies provide some evidence that the p.L485F variant may impact protein function (PS3; PMID: 18413255). The variant is located in the BRAF gene, which has been defined by the ClinGen RASopathy Expert Panel as a gene with a low rate of benign missense variants and pathogenic missense variants are common (PP2; PMID: 29493581). Additionally, computational prediction tools and conservation analysis suggest that this variant may affect the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. Rasopathy-specific ACMG/AMP criteria applied (PMID:29493581): PS4_Moderate, PS2, PS3, PM2, PP2, PP3.

Met criteria codes

PS2



PubMed:19206169

PS3



PMID 18413255: Kinase activities of selected B-Raf missense CFC mutations are compared to known B-Raf mutations found in cancer. Empty vector, wildtype B-Raf (WTB-Raf) or the indicated B-Raf point mutants were transfected in 293Tcells, and B-Raf activity was measured on Flag-immunoprecipitates using a coupled MEK-ERK-MBP phosphorylation assay. L485F showed increased kinase activity compared to WT

PubMed:18413255

PS4_Moderate



LMM unpublished (SCV000197149.4) + PMID: 16474404

PubMed:16474404

PP2



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP3



REVEL: .757, no predicted splicing impact, evolutionarily conserved

PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
Not Met criteria codes			
PM5			ClinVar 40370 (Likely Path)

Curation History 			
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